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UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 C.F.R. § 1.53(b))

Attorney Docket No.

PC 9942A

First Named Inventor or Application Identifier

C. K. CHIU

Title

PROCESS FOR PREPARING NAPHTHYRIDINONES AND ITS
INTERMEDIATES

Express Mail Label No.

EL162026898 US

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents.

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1. ☒ *Fee Transmittal Form (e.g., PTO/SB/17)
(Submit an original, and a duplicate for fee processing)
2. ☒ Specification [Total Pages 15]
(preferred arrangement set forth below)
- Descriptive title of the Invention
 - Cross References to Related Applications
 - Statement Regarding Fed sponsored R&D
 - Reference in Microfiche Appendix
 - Background of the Invention
 - Brief Summary of the Invention
 - Brief Description of the Drawings (if filed)
 - Detailed Description
 - Claim(s)
 - Abstract of the Disclosure
3. ☐ Drawing(s) (35 U.S.C. 11.3) [Total sheets]
4. ☐ Oath or Declaration [Total pages]
- a. ☐ Newly executed (original or copy)
- b. ☐ Copy from a prior application (37 CFR § 1.63(d))
(for continuation/divisional with Box 17 completed)
[Note Box 5 below]
- i. ☐ **DELETION OF INVENTOR(S)**
Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. §§ 1.63(d)(2) and 1.33(b).
5. ☐ Incorporation By Reference (useable if Box 4b is checked)
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered to be part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Microfiche Computer Program (Appendix)
7. ☐ Nucleotide and/or Amino Acid Sequence Submission (if applicable, all necessary)
- a. ☐ Computer Readable Copy
- b. ☐ Paper Copy (identical to computer copy)
- c. ☐ Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. ☐ Assignment Papers (cover sheet & document(s))
9. ☐ 37 C.F.R. § 3.73(b) Statement ☐ Power of Attorney
(when there is an assignee)
10. ☐ English Translation Document (if applicable)
11. ☐ Information Disclosure Statement (IDS)/PTO-1449 ☐ Copies of IDS Citations
12. ☐ Preliminary Amendment
13. ☒ Return Receipt Postcard (MPEP 503)
(Should be specifically itemized)
14. ☐ *Small Entity ☐ Statement filed in prior application, Status still proper and desired (PTO/SB/09-12)
15. ☐ Certified Copy of Priority Document(s) (if foreign priority is claimed)
14. ☐ Other: _____

*NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

17. If a CONTINUING APPLICATION, check appropriate box, and supply the requisite information below and in a preliminary amendment:
- ☐ Continuation ☐ Divisional ☐ Continuation-in-part (CIP) of prior application No: _____

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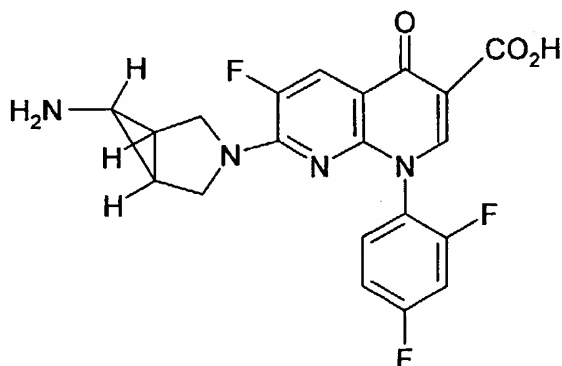
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Signature	<i>Bryan C. Zielinski</i>	Date	1/25/99

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A PROCESS FOR PREPARING NAPHTHYRIDONES AND INTERMEDIATES

This invention relates to a process for preparing the naphthyridone carboxylic acid, trovafloxacin and derivatives thereof, and intermediates of use therein.

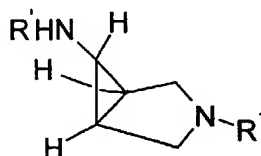
Trovafloxacin has the formula



VII

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as disclosed in U.S. Patent No. 5,164,402. The patent also discloses processes for making the compound by using an intermediate of the formula

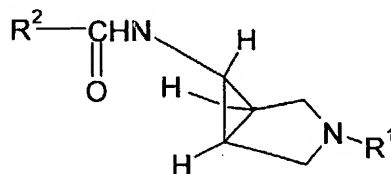


wherein R' is a nitrogen protecting group, such as tertiary butyloxycarbonyl.

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U.S. Patent No. 5,475,116 discloses the preparation of other intermediates for use in preparing the naphthyridones of U.S. Patent No. 5,164,402.

The present invention relates to a process for preparing a compound of the formula



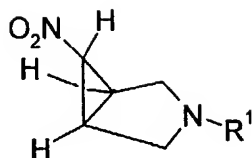
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wherein R¹ is benzyl, wherein the phenyl of the benzyl may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, and

R² is C₁-C₆ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, which comprises

(a) reducing a compound of the formula

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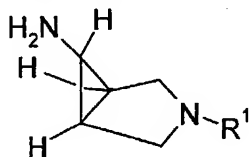


II

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wherein R^1 is as defined above, in the presence of iron and a organic solvent under acidic conditions, and

(b) acylating the compound of formula III formed:

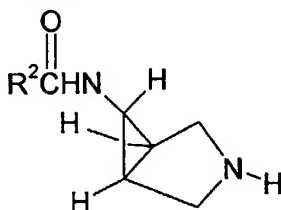


III

10 with an acylating agent of the formula $R^2C(O)X$ wherein R^2 is as defined above, and X is a leaving group.

In a preferred embodiment of the invention, the compound of formula III formed in step (a) is not isolated before acylation step (b).

The invention is further related to a process for preparing a compound of the formula



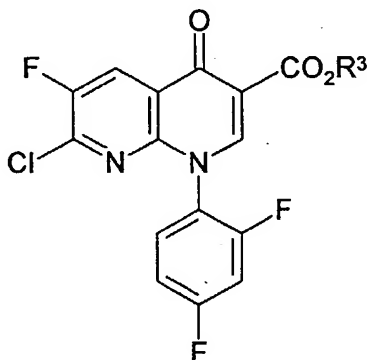
IV

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by debenzylating the compound of formula I wherein R^1 and R^2 are as defined above.

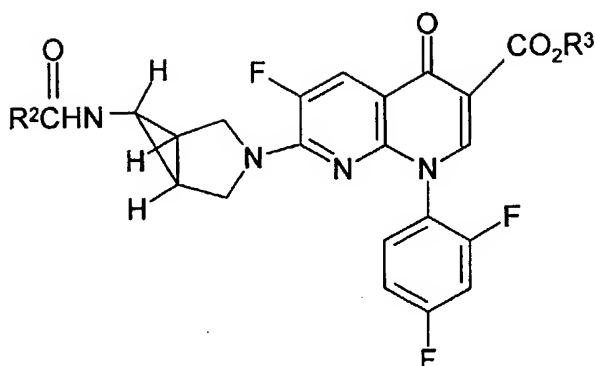
In a preferred embodiment, the debenzylation is carried out by reacting a compound of formula I with hydrogen and palladium catalyst in acetic acid and an organic solvent.

20 The invention also relates to reacting a compound of the formula IV with a compound of the formula



V

wherein R^3 is C_1 - C_8 alkyl, to form a compound of the formula



VI

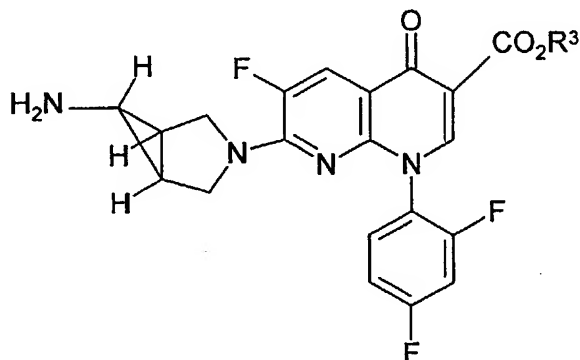
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wherein R² is as defined above with reference to formula I.

The invention relates to hydrolyzing the compound of formula VI with methanesulfonic acid, water and an organic solvent to form the monomethanesulfonic acid salt of the compound of the formula VII, trovafloxacin.

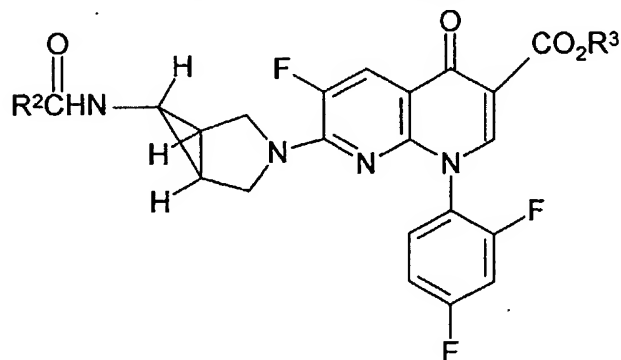
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The invention also relates to hydrolysis of the compound of formula VI with methanesulfonic acid and R³OH wherein R³ is as defined above to form the monomethanesulfonic acid salt of the compound of the formula



VIII

The invention further relates to the intermediates of the formulae



VI

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wherein R² is C₁-C₈ alkyl, trifluoromethyl, or phenyl which may be substituted by one or more of C₁-C₆ alkyl, C₁-C₆ alkoxy, halo, nitro, amino or trifluoromethyl, and

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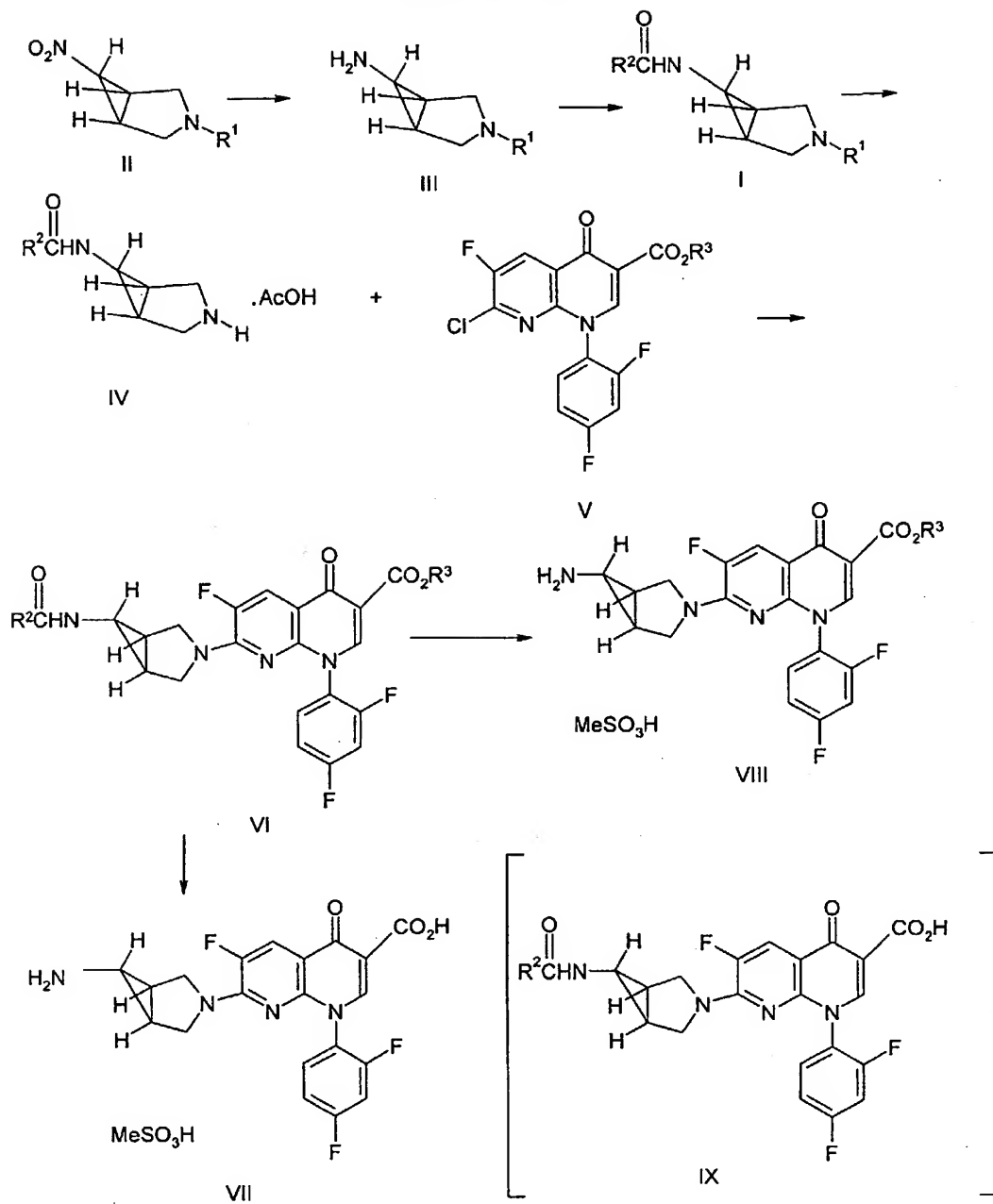


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Reaction Scheme



5 The compound of formula III is prepared from the corresponding compound of
formula II by reduction in the presence of iron and an organic solvent under acidic conditions.
The organic solvent is a C₁-C₆ alcohol, such as ethanol, or an ether such as tetrahydrofuran
(THF), and preferably, an alcohol. The acidic conditions are obtained by use of a mineral
acid, such as hydrochloric acid, or an organic acid, such as acetic acid (AcOH). Acetic acid is
10 preferred since it generally results in increased yields.

 The compound of formula III may then be isolated from the reaction mixture or may
be reacted further in situ, without isolation from the reaction mixture. In either case, the
further processing is by acylation with an acylating agent of the formula R²C(O)X to form the
compound of formula I. The leaving group X is conveniently a halogen, such as chloro, or the
15 acetoxo group. If the compound of formula III is first isolated, then the acylation may be
conducted under conventional acylating conditions, for instance, in the presence of an organic
solvent of the type discussed above.

 The compound of formula I is subjected to debenzylation to form the compound of
formula IV. It is understood that in the context of the invention, debenzylation includes
20 removal of R¹ wherein R¹ is benzyl or substituted benzyl. The reaction proceeds in
accordance with conventional debenzylation of tertiary nitrogen, conveniently by use of
hydrogen and palladium catalyst in acetic acid, and in an organic solvent. The organic solvent
may be a C₁-C₆ alcoholic solvent, such as ethanol, ethyl acetate, THF or water, or a mixture
thereof, such as ethanol and water.

25 The compound of formula VI is obtained by coupling the corresponding compound of
formula IV with the bicyclic intermediate ester of formula V. This coupling reaction may be
conducted with or without a solvent. The solvent, when used, must be inert under the reaction
conditions. Suitable solvents are ethyl acetate, acetonitrile, tetrahydrofuran, ethanol,
chloroform, dimethylsulfoxide, pyridine, and water, and mixtures thereof.

30 The reaction temperature usually ranges from about 20°C. to about 150°C.

 The reaction may advantageously be carried out in the presence of an acid acceptor
such as an inorganic or organic base, e.g. an alkali metal or alkaline earth metal carbonate or
bicarbonate, or a tertiary amine, e.g. triethylamine, pyridine or picoline.

35 The mesylate salt of the compound of formula VII, trovafloxacin, is formed by
hydrolysis of the compound of formula VI with methanesulfonic acid, water and an organic
solvent. Examples of suitable organic solvents include a C₁-C₆ alcohol, acetone, dimethoxy
ethane, glyme, THF, N-methyl-pyrrolidinone, and water, and mixtures thereof.

 The mesylate salt of the compound of formula VIII is obtained by hydrolysis of the
compound of formula VI with methanesulfonic acid and a C₁-C₆ alcohol of the formula R³OH,
40 for example ethanol. The compound of formula VIII is an intermediate in the preparation of
the mesylate salt of a prodrug of trovafloxacin wherein the amino group is substituted by an
amino acid or a polypeptide, e.g. dipeptide, as disclosed in U.S. Patent No. 5,164,402.

5 The compound of formula IX in the Reaction Scheme is the intermediate formed in the reaction from compound VI to VII.

 The compound of formula VII and the mesylate salt thereof (the active compounds) are useful in the treatment of bacterial infections of broad spectrum, particularly the treatment of gram-positive bacterial strains.

10 The active compounds may be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally or in the form of tablets containing such excipients as starch or lactose, or in capsules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing
15 flavoring or coloring agents. In the case of animals, they are advantageously contained in an animal feed or drinking water in a concentration of 5-5000 ppm, preferably 25-500 ppm. They can be injected parenterally, for example, intramuscularly, intravenously or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which can contain other solutes, for example, enough salt or flucose to make the solution
20 isotonic. In the case of animals, compounds can be administered intramuscularly or subcutaneously at dosage levels of about 0.1-50 mg/kg/day, advantageously 0.2-10 mg/kg/day given in a single daily dose or up to 3 divided doses.

 The invention also provides pharmaceutical compositions comprising an antibacterially effective amount of a compound of the formula (I) together with a
25 pharmaceutically acceptable diluent or carrier.

 The compounds of the invention can be administered to humans for the treatment of bacterial diseases by either the oral or parenteral routes, and may be administered orally at dosage levels of about 0.1 to 500 mg/kg/day, advantageously 0.5-50 mg/kg/day given in a single dose or up to 3 divided doses. For intramuscular or intravenous administration, dosage
30 levels are about 0.1-200 mg/kg/day, advantageously 0.5-50 mg/kg/day. While intramuscular administration may be a single dose or up to 3 divided doses, intravenous administration can include a continuous drip. Variations will necessarily occur depending on the weight and condition of the subject being treated and the particular route of administration chosen as will be known to those skilled in the art.

35 The following Examples illustrate the invention. The abbreviations used mean the following: GC=gas chromatography; MS=mass spectrometry; TLC=thin layer chromatography, HPLC = high performance liquid chromatography; LCMS = liquid chromatography mass spectrometry; and NMR = nuclear magnetic resonance.

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Example 1

(1 α , 5 α , 6 α)-6-Acetamido-3-benzyl-3-azabicyclo[3.1.0]hexane

A 3-necked round bottom flask, equipped with a thermometer, a overhead stirrer and a condenser with nitrogen purge, was charged with 768 g of nitrocyclopropane, 5.75 L of isopropanol (7.5 volumes), 1.79 L of acetic acid (9.1 equivalents) and 1153 g of iron powder (6
10 equivalents). The reaction mixture was heated at 50°C until the reaction was completed by GC/MS analysis (about 6 hours). 448 mL of acetic anhydride (1.4 equivalents) was added and stirred at 50°C for 15 minutes before cooling. The reaction mixture was diluted with 8 L isopropanol (10.5 volumes) and stirred for 30 minutes. The residual iron was filtered off and the cake washed with 11.25 L of isopropanol (15 volumes). The isopropanol solution was
15 concentrated in vacuo to an oil, 18 L of dichloroethane (24 volumes) was added before bringing the pH to 12 with 8.8 L of 5% sodium hydroxide solution (about 12 volumes). The layers were separated and the separated organic layer was dried by magnesium sulfate. The resulting dark amber oil was treated with 7.5 L of hexanes (10 volumes) and granulated at 25°C before collecting the product as a white solid. Drying at 50°C under vacuum gave 610 g
20 of the title compound (77 % yield). Analysis was done by GC/MS, NMR and TLC.

Example 2

(1 α , 5 α , 6 α)-6-Acetamido-3-azabicyclo[3.1.0]hexane

A Parr Bottle was charged with 150 g of the compound of Example 1, 112 mL of acetic acid (3 equivalents), 1.5 L of methanol (10 volumes) and 15 g of (10% by wt. 50% wet)
25 Pd/C catalyst (0.1 equivalent). The bottle was purged with nitrogen and then brought to 50 psi pressure with hydrogen. The mixture was shaken for 48 hours and recharged with catalyst as necessary during the debenzylation reaction. After TLC indicated that the reaction was complete, the catalyst was filtered off, and the filtrate was concentrated in vacuo to an oil. 3 L of ethyl acetate (20 volumes) was added to the oil, and granulated for an hour. The solid was
30 collected by filtration and dried under vacuum at 50°C to provide 107 g of the title compound (82 % yield) as the acetic acid salt.

Example 3

(1 α , 5 α , 6 α)-7-(6-acetamido-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, ethyl ester

A reaction flask was charged with 241.9 g of 7-chloro-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester, 151.6 g of the acetic acid salt of the compound of
35 Example 2 (1.2 equivalents), 2661mL of ethyl acetate (11 volumes) and 220 mL of triethylamine (2.5 equivalents). The mixture was heated at refluxing temperature under nitrogen for 6 hours monitored by HPLC or LCMS. After the reaction was completed, the reaction mixture was cooled to ambient temperature. Water (11 volumes) was added and the
40 biphasic mixture was stirred for 17 hours. The white solid was collected by filtration, washed

- 5 with 2661 mL of water (12 volumes) and oven dried at 50°C to provide 292 g of the title compound (95 % yield).

Example 4

- In a reaction flask, 220 g of the compound of Example 3, 1.76 L of n-butanol (8 volumes), 1.54 L of water (7 volumes) and 141 mL of 70% methanesulfonic acid (3.0 equivalents) were mixed. The mixture was heated at reflux for 21 hours, and the reaction was monitored by HPLC or LCMS. After complete reaction, the mixture was cooled to 50°C and filtered to make it speck-free. The filtrate was cooled to 0-5°C and granulated for 2 hours. The solid was collected by filtration, washed with 220 mL of water (1 volume) and 660 mL n-butanol (3 volumes). The wet cake was mixed with 660 mL of n-butanol (3 volumes), seeded with 0.1 gm of the desired polymorph and heated to 95-100°C. After complete polymorph conversion, in approximately 2 hours, the mixture was cooled to ambient temperature. The solid was filtered, washed with 100 mL of n-butanol (0.5 volumes) and dried in a nitrogen atmosphere to provide 200 g of (1 α , 5 α , 6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid, monomethanesulfonate (87% yield).

Example 5

- 0.8 mL of methanesulfonic acid (2.7 equivalents) was added dropwise to a solution of 2.2 g of the compound of Example 3 in 10 mL of ethanol (4.5 volumes). The resulting reaction mixture was heated at refluxing temperature for 40 hours, monitored by GCMS. After the reaction was completed, it was diluted with ethyl acetate (20 mL) and washed with (3x 10mL) 1M sodium hydroxide solution. The organic layer was separated, dried over anhydrous magnesium sulphate and filtered. The filtrate was concentrated in vacuo to provide 1.37 g of (1 α , 5 α , 6 α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester, monomethanesulfonate (96% yield).